Malignant Lymphoma of the Breast

A Study of 53 Patients

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Fifty-three patients with non-Hodgkin's lymphoma of the breast were reviewed and classified using four current classifications of lymphoma. All patients were female with a mean age of 57 years. The majority of patients had histiocytic or large-cell lesions and presented as clinical Stage I. The tumors were described clinically as primary in the breast, and mammary parenchyma was found in 79% of the diagnostic biopsy specimens. The other specimens showed lymphoma in mammary adipose tissue. Survival was not influenced by the presence or absence of breast parenchyma in the biopsy. Statistically significant survival differences were found to be related to stage at presentation as well as to tumor grade, using Kiel and Working Formulation categories. Patients with Stage I disease and those with low-grade lesions had a more favorable prognosis. No discernible factors, including stage or histologic findings, appeared to affect the recurrence rate.

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PRIMARY LYMPHOMAS OF THE BREAST are infrequent neoplasms. To date, approximately 200 patients have been reported in the literature with rarely more than 20 patients in any study. Use of different classification schemes, as well as variability in staging and treatment, contribute to conflicting conclusions about this disease. We present an assessment of 53 patients with non-Hodgkin's lymphoma of the breast in the context of four current systems of pathologic classification.

Materials and Methods

Sixty-one patients with malignant lymphoma (ML) of the breast were recorded in Memorial Sloan-Kettering Cancer Center (MSKCC) between 1949 and 1984. On review of all data, 8 patients were excluded for the following reasons: (1) unavailability of histologic material for review (3 patients), (2) tumor limited to axillary lymph nodes rather than breast (2 patients), (3) tumor involving only the chest wall (1 patient), and (4) lack of clinical information (2 patients). Included in this study were 12 patients treated at hospitals other than MSKCC whose slides were seen in consultation. These 53 patients represent the object of this study.

The patients in this study had no diagnosis of lymphoma before the diagnostic breast biopsy. Patients who initially had clinical evidence of lymphoma at sites other than breast or breast and axilla (*e.g.*, chest wall) and those with lymphoma limited to the axillary lymph nodes were excluded. Women with lesions believed clinically to be in the breast were included even if the biopsy results showed adipose tissue but no mammary glandular parenchyma. Although the main object of this work was to study lymphomas of the breast in Stages I and II as a distinct clinical problem, we included patients with disseminated lymphoma (Stages III and IV) in order to compare this study with previously published studies.

Patients were staged at the time of initial diagnosis using the Ann Arbor staging system as applied to primary extranodal lymphoma.[1] The following stages were described: Stage I, involvement of breast; Stage II, involvement of breast and ipsilateral axillary lymph nodes; Stage III, involvement of breast and lymph nodes on both sides of the diaphragm; and Stage IV, involvement of breast and other extranodal sites with or without associated lymph node involvement.

The histologic sections stained with hematoxylin and eosin had been fixed in various ways, most commonly in 10% formalin or B_3. The slides were reviewed by three pathologists and classified according to four systems: Rappaport,[2] Lukes-Collins,[3] Kiel, as reported by Lennert,[4] and the Working Formulation.[5] In some patients, additional studies such as electron microscopy and cell surface markers had been performed, but these were too infre-

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quent to permit analysis. Clinical information, including initial staging data, was obtained from hospital charts or external sources.

Survival curves and recurrence-free survival curves were computed as Kaplan–Meier estimates from incomplete data.[6] Statistical comparisons of survival data were performed using the Gilbert and Gehan test (a modification of Wilcoxon's test for incomplete data), and the logrank test.[7] The latter test gives more conservative results. Patients who died of causes other than breast lymphoma were treated as lost to follow-up. The age at diagnosis distributions were compared using the two-sample Kolmogorov-Smirnov test.[8] Absence of statistically significant difference between two survival patterns may be the result of either true absence of difference or small size of the statistical sample.

Results

Clinical Features

All patients were female. The range of age at diagnosis for all 53 patients was 21–86 years (mean: 57.3 years). The median age was 60 years, with the interquartile range from 40–69 years. The single largest group were in their sixties (14 patients, 26%). The right breast was involved in 31 patients (60%) and the left breast in 20 patients (39%), a difference that was not statistically significant. One patient had bilateral disease. Laterality was unknown in one patient.

Symptoms were reported in 45 patients. The majority of patients (42 patients, 93%) had a painless mass. Other symptoms were painful mass in two patients (4%) and breast swelling in one patient (2%). Clinical tumor size, reported in 37 patients, ranged from 1–12 cm (mean: 3 cm). Only 11 tumors (30%) were 2 cm or less in diameter (T_1), whereas 22 tumors (59%) were between 2.1 and 5 cm (T_2). Three lesions were described as "large masses" and one was described as a "small mass." The distribution of extent of disease (stage) at initial presentation was as follows: 54% were Stage I, 28% were Stage II, 2% were Stage III, and 16% were Stage IV.

A second primary neoplasm, excluding basal cell and squamous carcinoma of the skin, was detected in eight of 46 patients (17%) for whom information was available (Table 1). There were two cases each of carcinoma of the colon and cutaneous malignant melanoma.

TABLE 1. *Other Malignant Tumors Diagnosed in Patients Treated for Breast Lymphoma*

Tumor Type	Temporal Relationship to Lymphoma
Carcinoma of colon	5 years before lymphoma
Carcinoma of colon	Several months before lymphoma
Cutaneous melanoma *in situ*	Before lymphoma (date unknown)
Cutaneous malignant melanoma	Simultaneous with lymphoma
Hodgkin's disease	30 years before lymphoma
Papillary bladder carcinoma	Date unknown
Papillary thyroid carcinoma	15 years after lymphoma
Carcinoid tumor (lung)	11 years after lymphoma

Treatment and Follow-up

Primary surgical treatment was reported as follows: radical mastectomy in 13 patients (25%); modified radical mastectomy in four patients (8%); simple mastectomy in one patient (2%), excisional biopsy in 17 patients (32%); excisional biopsy and lymph node biopsy in three patients (5%), and biopsy only in 15 patients (28%).

Four of 18 patients who had mastectomy also received radiation and chemotherapy, four patients received only radiation, and two patients received only chemotherapy. Radiation therapy was administered to 20 of the 35 patients who had limited resection, five patients received chemotherapy, and two patients received both radiation and chemotherapy. Six patients were treated by excision of the tumor only. Data on additional treatment were unavailable for two patients.

Follow-up data were available for 52 patients. The mean follow-up time (from diagnosis to death due to any cause or date of last follow-up) was 4 years 9 months with a mean of 3 years 6 months and an interquartile range from 1 year 7 months to 7 years. The overall range was from 42 days to 25 years 10 months.

Survival rate for all stages was 74% at 5 years and 42% at 10 years with a recurrence-free survival rate of 38% at 5 years and 33% at 10 years (Fig. 1).

Survival for Stages I and II are compared in Figure 2 with the difference being statistically significant ($p = 0.01$ Gilbert-Gehan; $p = 0.05$ logrank). This difference remained statistically significant even when 5 patients with Stage I nodular lymphoma were excluded. The 5-year survival rate for Stage I was 89% and 10-year survival rate was 42%. Fifty per cent of patients with Stage II disease survived 5 years. There were no additional deaths between 5 and 10 years in these remaining six patients with Stage II disease. There was no statistically significant difference between survival curves for Stages II, III, and IV.

An analysis of recurrence-free survival is presented in Figure 3. Patients with Stage I disease had delayed recurrences but ultimately had a relapse rate approaching that of patients whose initial presentation was Stage II or more advanced. The distribution of patterns of recurrence among these groups did not differ significantly.

Pathology

Examination of histologic material revealed tumor cells densely and uniformly infiltrating the breast tissue. Whereas the tumor mass appeared well-circumscribed

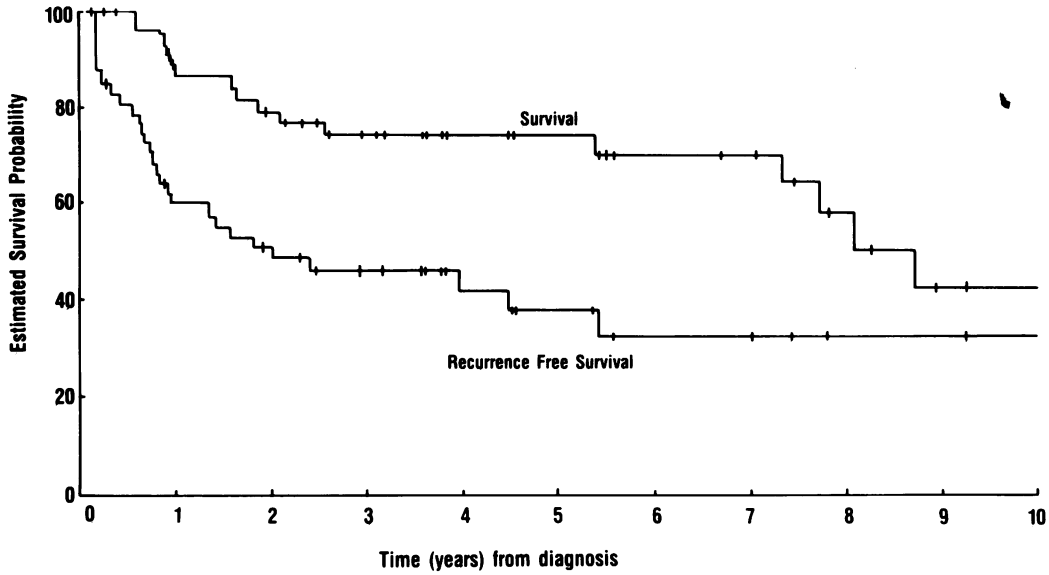

FIG. 1. Estimated probabilities of survival and recurrence-free survival from breast lymphoma (based on all available patients), for given time from diagnosis. Jumps in the curves correspond to deaths due to breast lymphomas. Vertical ticks on the curves represent the maximum follow-up times of patients either when last seen alive or when dead of other causes.

grossly, the lymphoma cells irregularly infiltrated the parenchyma at the periphery of the mass for a variable distance. A reactive lymphoid infiltrate composed primarily of small lymphocytes was often seen surrounding the lesion. Germinal centers were sometimes noted within this reactive infiltrate.

An interesting observation in a small number of patients was an unusual pattern of lymphomatous infiltration in mammary ductules and acini. The malignant lymphoid cells expanded the structures and infiltrated the epithelial cell layer. As a consequence the lining epithelial cells were often clustered in the lumen, simulating lobular carcinoma. Staining of the involved breast tissue with an antikeratin antibody made it possible to distinguish infiltrating lymphomatous cells from the residual epithelial component (Fig. 4).

All patients were considered clinically to have lymphoma involving the breast. Initial biopsy specimens from 42 patients (79%) showed lymphomatous infiltration of mammary parenchyma, whereas in 11 patients (21%) the sample consisted of adipose tissue. Patients with parenchymal involvement seen histologically did not differ significantly from the remainder with respect to stage or histologic findings in any of the classification schemes. There was no difference in survival or recurrence-free survival between patients whose results of breast biopsy showed lymphoma in glandular parenchyma and those whose biopsy results showed lymphoma only in mammary fat.

The distribution of patients in the four classification schemes studied is shown in Table 2. The distribution of lymphomas within the classifications was studied in relation to stage at diagnosis. In the Rappaport classification,

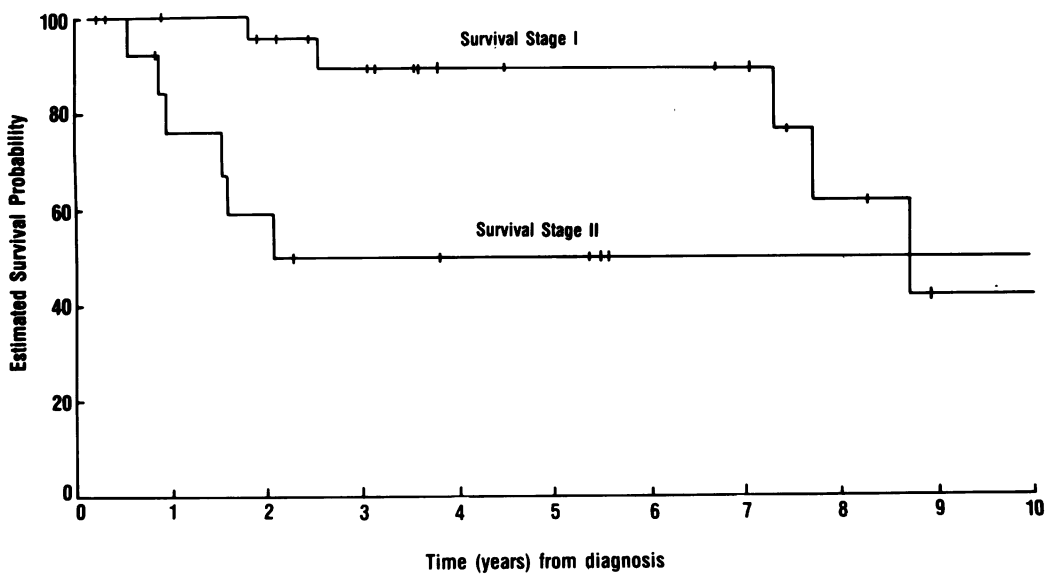

FIG. 2. Estimated probabilities of survival from breast lymphoma: Stage I *versus* Stage II. For details, see legend to Figure 1.

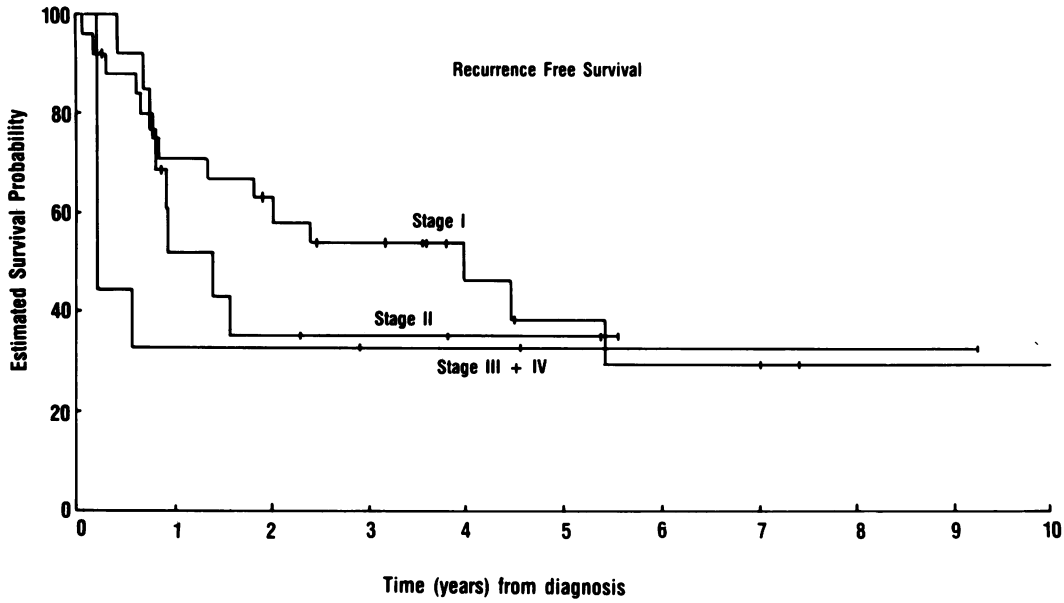

FIG. 3. Estimated probabilities of recurrence-free survival from breast lymphoma: Stage I *versus* Stage II, Stage I *versus* Stages III and IV. For details, see legend to Figure 1.

there was a relatively higher proportion of mixed lymphomas in Stage I than in the other stages (Table 3). Five patients with nodular mixed lymphoma were among the 26 patients with Stage I disease.

To assess the influence of histologic type on survival, patients with Stage I disease with diffuse histiocytic lymphoma (DHL), diffuse mixed lymphoma (DML), and diffuse poorly differentiated lymphocytic lymphoma (DPDL) were compared. Overall and recurrence-free survival differences between the different histologic types were not statistically significant. Among patients with DHL, those with Stage I disease appeared to have a better prognosis than did patients with Stage II disease, but the difference was not statistically significant. There was no apparent difference between Stages II, III, and IV. There were too few patients with DML and DPDL to compare Stage I with Stages II, III, and IV in these forms of lymphoma.

A comparison of survival curves for low- and high-grade Stage I and II lymphomas following the Kiel classification suggests an appreciably better outcome for patients with low-grade lesions. This proved to be statistically significant by the Gilbert-Gehan test ($p = 0.05$). Low-grade lesions had a longer recurrence-free interval. An analysis using the Working Formulation revealed a similar difference in survival between low- and intermediate-grade lymphomas ($p = 0.05$, Gilbert-Gehan test).

Various subgroups of patients were compared with respect to the effect of treatment on survival and recurrence. For example, patients with Stage I and Stage II disease were grouped into those patients treated with lumpectomy or mastectomy alone (11 patients) and those patients treated with lumpectomy or mastectomy supplemented by chemotherapy, radiotherapy, or both (18 patients). This same comparison was further limited to patients with Stage I disease only (8 *vs.* 11 patients, respectively). Also, patients with Stage I disease and Stage I and Stage II disease were compared with respect to any single treatment modality (chemotherapy *vs.* no chemotherapy, *etc.*). No significant or even apparent differences for either survival or recurrence-free survival were found in any of these tests.

Patient outcome was related to tumor size at presentation. The masses were divided into two equal groups smaller and larger than the mean, which was 3 cm. There was a difference in 5-year survival (larger tumors: 67%, smaller tumors: 92%), although this difference was not statistically significant.

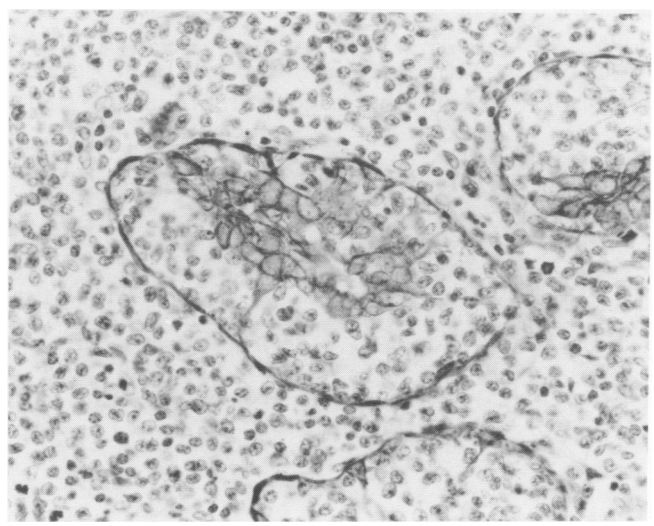

FIG. 4. Malignant lymphoma infiltrating breast tissue. Wide-spectrum antikeratin antibody (avidin–biotin complex technique).

TABLE 2. *Distribution of Mammary Lymphomas According to Four Classification Schemes*

Rappaport N = 53	Kiel N = 53	Lukes-Collins N = 53	Working Formulation N = 53
DWDL (2)	Lymphoplasmacytoid immunocytoma (2)	Small lymphocyte (1)	Small lymphocyte (1)
NPDL (1)	Lymphocytic (CLL type) (1)	Plasmacytoid lymphocyte (2)	Small lymphocyte, plasmacytoid (2)
DPDL (11)	Centrocytic diffuse (3)	Small cleaved follicular (4)	Small cleaved follicular (1)
NML (7)	Centroblastic-centrocytic follicular and diffuse (3)	Small cleaved follicular and diffuse (1)	Small cleaved follicular and diffuse (0)
DML (5)	Centroblastic-centrocytic diffuse (24)	Small cleaved diffuse (8)	Small cleaved diffuse (9)
DHL (26)	Centroblastic follicular (5)	Large cleaved follicular (1)	Mixed cells follicular (4)
UD (1)	Centroblastic diffuse (11)	Large cleaved follicular and diffuse (2)	Mixed cells follicular and diffuse (3)
	Centroblastic polymorphous (2)	Large cleaved diffuse (18)	Mixed cells diffuse (5)
	Lymphoblastic B (1)	Large noncleaved diffuse (14)	Large cleaved diffuse (12)
		Small noncleaved cell (1)	Small noncleaved cell (1)
		Diffuse large noncleaved (14)	
	Unclassifiable (1)	Unclassifiable (1)	Unclassifiable (1)

The same number of patients were diagnosed before and including 1977 as were after 1977. There were only slight differences in survival between these two groups.

Discussion

Clinical Features

Our review of the literature revealed 207 cases of mammary lymphoma reported from 1930–1985.[9–22] It is, therefore, not surprising that lymphoma is rarely considered in the preoperative evaluation of patients with a breast tumor. Analysis of our 53 patients did not reveal any unusual clinical features that would lead one to consider a diagnosis of lymphoma clinically when the breast is the site of initial presentation.

The age at diagnosis distribution of our patients (median: 60 years) is virtually identical (Smirnov-Kolmogorov test) to the respective age distribution for adenocarcinoma of the breast (median: 58 years, from a sample of 550 patients).[23] The predominance of right-sided lesions, 60% in our study, has been noted by others as well. Although we had too few patients for this difference to be statistically significant, when added to patients from multiple studies,[9–22] the right-sided predominance was highly significant ($p = 0.005$). This is in contrast to a well-documented left-sided predominance for all types of breast carcinoma.[24]

Mammary lymphomas tend to be larger at diagnosis than adenocarcinomas. Our study demonstrated a mean size of 4 cm with 41% of patients having tumors between 4.5 and 7.5 cm. In a recent review of breast carcinoma treated at Memorial Hospital, only 18% of primary tumors were 4 cm or larger.

Classification of lymphomas (Table 2). Twenty-six of 53 tumors were classified as DHL according to the Rappaport classification. There were also 12 mixed lymphomas (7 nodular, 5 diffuse), 11 DPDL, one nodular poorly differentiated lymphoma (NPDL), two diffuse well-differentiated lymphomas (DWDL), and one undifferentiated lymphoma (UD). These results differ from with those of Mambo et al.[9] who found eight examples of UD among 14 patients. The distribution of tumor types in our study resembled that of Schouten et al.[10] and that of Lattes.[13] In the latter study, 28 of 38 tumors were described as "reticulum cell sarcomas." Hodgkin's disease occurs very rarely as a primary tumor of the breast,[10] and no cases of this occurred in our study.

Comparison of breast lymphoma with other extranodal lymphomas[1] reveals a similar breakdown of subtypes using the Rappaport classification except for a relative lack of mixed lymphomas when compared with our findings.

TABLE 3. *Distribution of Stage at Diagnosis Related to Histologic Type of Lymphoma*

Rappaport Classification	Stage at Presentation I	II	III	IV	Total
NML	5	1	0	0	6
NPDL	0	0	1	0	1
NHL	0	0	0	0	0
DHL	12	10	0	3	25
DML	4	0	0	0	4
DPDL	5	3	0	3	11
DWDL	0	0	0	1	1
UD	0	0	0	1	1
Total	26	14	1	8	49

TABLE 4. *Survival Rates In Mammary Lymphoma*

	No. of Patients	Survival (%) 2 yr	5 yr	10 yr
Current study	48*	79%	74%	42%
Tanaka et al.[15]	48	65%	51%	51%
Combined data from 4 studies[9–11,16]	53	57%	48%	41%

* Cause of death not known in 5 cases.

This may reflect differing criteria for the percentages of small and large cells needed to diagnose a mixed lymphoma.

Only two of 53 patients had a lymphoplasmacytoid lymphoma (Kiel classification). This type is found more frequently in other extranodal sites, constituting 36% of gastrointestinal lymphoma,[25] 28% of gastric lymphoma,[26] and 58% of pulmonary lymphoma.[27] A hypothesis offered as to the frequency of occurrence of lymphoplasmacytoid tumors in gastrointestinal tract and lung suggests a possible role of mucous-producing glandular epithelium in B cell differentiation. This may explain the lack of lymphoplasmacytoid lesions in the breast.

Prognosis. Survival statistics published in various sources are difficult to compare since authors use different indices of survival. However, several papers contained sufficient data to enable us to compute Kaplan–Meier survival estimates. To compare our results with those of others we examined two sets of data, that of Tanaka et al.[15] and the combined studies of Mambo et al.,[9] Schouten et al.,[10] DeCosse et al.,[11] and Wiseman and Liao.[16]

A comparison with our own survival data is presented in Table 4. Five-year survival rate using the data of Tanaka et al.[15] is 51%. Similarly, combined group data[9–11,16] yields a 5-year survival rate of 48%. This is significantly different ($p = 0.01$) from the 74% 5-year survival rate yielded by our data. This difference is no longer seen at 10 years where our patients had a 42% survival rate compared with 51% in the study of Tanaka et al.[15] and 41% for the combined group data.[9–11,16]

There are probably several reasons for the improved 5-year survival rates, but one key importance is differences among the studies in clinical stage at diagnosis. Only 19% of our patients had disseminated (Stages III and IV) disease. In contrast, 70% of the patients described in the study of Mambo et al.[9] had advanced stages. Similarly, over 50% (7 of 13 patients) described by Schouten et al.[10] had Stages III and IV disease. Many others[13,15,16] do not address the problem of staging.

When survival rates for Stages I and II were compiled from the combined data of several studies[9–11] the results did not differ significantly from the survival of patients in our study with comparable stages of disease (Table 5).

We were unable to assess the relative influence of histologic type of lymphoma on survival because the majority of tumors were of large cell or histiocytic type. The lack of undifferentiated lymphomas in our study contrasts with the high percentage (62%) of patients with this tumor type described in the study of Mambo et al.[9] Undifferentiated (Burkitt's) lymphoma is well known for its aggressive behavior and poor prognosis. Our only patient with undifferentiated lymphoma died 10 months after diagnosis. The difference in prognosis between our study and other studies is not related to a difference in the percentage of nodular lymphoma since the proportion of these lesions in our study was almost identical with that in the combined data from DeCosse et al.,[11] Schouten et al.,[10] Mambo et al.,[9] and Wiseman and Liao.[16]

TABLE 5. *Survival Rates in Stage I and Stage II Mammary Lymphoma*

	No. of Patients	Survival (%)			
		1 yr	2 yr	5 yr	10 yr
Current study	36	91%	81%	74%	41%
Combined data from 3 studies[9–11]	25	80%	72%	60%	47%

Our study demonstrated, however, in addition to stage, statistically significant differences in survival within Working Formulation and Kiel classification grades. No significant differences were shown using the Rappaport classification. These results suggest that tumor grade may be a useful factor in the assessment of prognosis.

We could not demonstrate any relationship between survival and treatment modality, tumor size, era of therapy, or infiltration of breast parenchyma. There were no discernible factors that influenced recurrence rate, including stage or histologic type, in early stage of disease. Absence of statistical significant differences may reflect either small sample size or a true lack of difference in survival. However, it is apparent from this study that clinical stage and histologic grade are the most significant prognostic factors for patients with primary lymphoma of the breast.

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